

EXHIBIT A

Povidone

1. Nonproprietary Names

BP: Povidone
PhEur: Polyvidonum
USP: Povidone

2. Synonyms

El201; *Kollidon*; *Plasdone*; poly[1-(2-oxo-1-pyrrolidinylethylene)]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3. Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer
[9003-39-8]

4. Empirical Formula Molecular Weight

$(C_4H_5NO)_n$ 2500-3 000 000
The USP XXII (Suppl 9) describes povidone as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10-120. The K-value is calculated using Fikentscher's equation⁽¹⁾ shown below:

$$\log z = c \left(\frac{75k^2}{1 + 1.5kc} \right) + k$$

where z is the relative viscosity of the solution of concentration c , k is the K-value $\times 10^3$, and c is the concentration in % w/v. Alternatively, the K-value may be determined from the following equation:

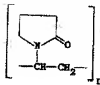
$$K - \text{value} = \frac{\sqrt{300c \log z + (c + 1.5c \log z)^2} + 1.5}{0.15c + 0.03c^2}$$

where z is the relative viscosity of the solution of concentration c , k is the K-value $\times 10^3$, and c is the concentration in % w/v. Approximate molecular weights for different povidone grades are shown below:

K-value	Approximate molecular weight
12	2500
15	8000
17	10 000
25	30 000
30	50 000
60	400 000
90	1 000 000
120	3 000 000

See also Section 8.

5. Structural Formula



6. Functional Category

Suspending agent; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations it is primarily used in solid dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol or hydroalcoholic solutions. Povidone solutions may also be used as coating agents.

Povidone is additionally used as a suspending, stabilizing or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Special grades of pyrogen free povidone are available and have been used in parenteral formulations, see Section 14.

Use	Concentration (%)
Carrier for drugs	10-25
Dispersing agent	up to 5
Eye-drops	2-10
Suspending agent	up to 5
Tablet binder, tablet diluent, or coating agent	0.5-5

8. Description

Povidone is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and exist as spheres. Povidone K-90 and higher K-value povidones are manufactured by drum drying and exist as plates.

9. Pharmacopeial Specifications

Test	PhEur 1990	USP XXII (Suppl 9)
Identification	+	+
pH	—	3.0-7.0
Appearance of solution	+	—
Water	≤ 5.0%	≤ 5.0%
Residue on ignition	—	≤ 0.1%
Sulfated ash	≤ 0.1%	—
Lead	—	≤ 10 ppm
Heavy metals	≤ 10 ppm	—
Aldehydes	≤ 0.2%	≤ 0.2%
Hydrazine	—	≤ 1 ppm
Vinylpyrrolidinone	≤ 0.2%	≤ 0.2%
K-value		
≤ 15	85.0-115.0%	85.0-115.0%
> 15	90.0-108.0%	90.0-108.0%
Nitrogen content	11.5-12.8%	11.5-12.8%

10. Typical Properties

Acidity/alkalinity:

pH = 3.0-7.0 (5% w/v aqueous solution)

Compressibility: see HPE Data.

Density: 1.17-1.18 g/cm³

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International Specialty Products, Inc.

1381 Alps Road Wayne NJ 07470 • Tel: 973-628-4000

R&D/QC Product Data Sheet Approved By:	
PLASDONE K-29/32	Part Number: PN 10004 Date: 21 MAR 09
SALES SPECIFICATIONS	
QC: [Signature] 7E NOV 00	

Chemical Description:

Polymer of 1-vinyl-2-pyrrolidone. Pharmaceutical Grade K-29/32

Specifications:

Appearance @ 25 deg. C	White to creamy white powder
Identification Tests (<u>Q237</u> & <u>W1125</u>)	Meets all ID tests
Appearance @ 25 deg. C (5% as is aqueous soln., <u>TC200135</u>)	Free of haze
+ European Color Test – B Color (<u>W731</u>)	B6 Minimum
+ European Color Test – BY Color (<u>W731</u>)	BY6 Minimum
+ European Color Test – R Color (<u>W731</u>)	R6 Minimum
% Moisture (Karl Fischer, <u>W623</u>)	5.0 Maximum
pH (5% as is aqueous solution, <u>Q231</u>)	3.0 - 5.0
% Ash (Residue on Ignition or Sulphated, <u>W720</u>)	0.02 Maximum
ppm Vinyl Pyrrolidone (HPLC, <u>W686</u>)	5.0 Maximum
% 2-pyrrolidone (<u>W1406</u>)	3.0 Maximum
ppm Heavy Metals (as Lead, <u>W719</u>)	5 Maximum
% Aldehydes (Calculated as acetaldehyde, <u>W652</u>)	0.05 Maximum

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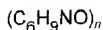
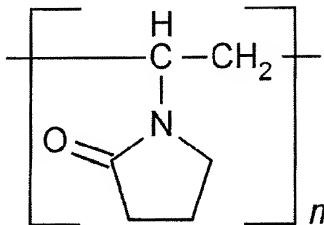
PLASDONE K-29/32

SALES SPECIFICATIONS

% Nitrogen (Solids Basis, <u>W1118</u>)	12.0 – 12.8
K-Value (Viscosity of 1% solids w/v aqueous solution, <u>W625</u>)	29 – 32
ppm Peroxide Content (Titanyl Sulfate Method, <u>W028</u>)	400 Maximum
ppm Hydrazine (<u>W403</u>)	1.0
Total Aerobic Plate Count, CFU/g (<u>Q200</u>)	100 Maximum
Mold/Yeast, CFU/g (<u>Q200</u>)	100 Maximum
Staphylococcus Aureus CFU/g (<u>Q200</u>)	Negative
Salmonella, CFU/g (<u>Q200</u>)	Negative
Pseudomonas aeruginosa, CFU/g (<u>Q200</u>)	Negative
E. coli, CFU/g (<u>Q200</u>)	Negative
+ B, BY or R color must be 6 minimum. Use appearance solution	
Material meets the requirements for Povidone in current US, European and Japanese Pharmacopeias.	

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Povidone



2-Pyrrolidinone, 1-ethenyl-, homopolymer.

1-Vinyl-2-pyrrolidinone polymer [9003-39-8].

» Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. The different types of Povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. (See the section on *K-value* below.) The K-value of Povidone having a stated (nominal) K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the stated values. The K-value of Povidone having a stated K-value or a stated K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the stated value or of the average of the stated range.

Packaging and storage— Preserve in tight containers.

Labeling— Label it to state, as part of the official title, the K-value or K-value range of the Povidone.

Identification—

A: To 10 mL of a solution (1 in 50) add 20 mL of 1 N hydrochloric acid and 5 mL of potassium dichromate TS: an orange-yellow precipitate is formed.

B: Dissolve 75 mg of cobalt nitrate and 300 mg of ammonium thiocyanate in 2 mL of water. To this solution add 5 mL of a solution of Povidone (1 in 50), and render the resulting solution acid by the addition of 3 N hydrochloric acid: a pale blue precipitate is formed.

C: To 5 mL of a solution (1 in 200) add a few drops of iodine TS: a deep red color is produced.

pH $\langle 791 \rangle$: between 3.0 and 7.0, in a solution (1 in 20).

Water, Method I $\langle 921 \rangle$: not more than 5.0%.

Residue on ignition $\langle 281 \rangle$: not more than 0.1%.

Lead (251) — Dissolve 1.0 g in 25 mL of water: the limit is 10 ppm.

Limit of aldehydes—

Phosphate buffer— Transfer 8.3 g of potassium pyrophosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N hydrochloric acid to a pH of 9.0, dilute with water to volume, and mix.

Aldehyde dehydrogenase solution— Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, dissolve in 10.0 mL of water, and mix. [NOTE— This solution is stable for 8 hours at 4° .]

NAD solution— Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, dissolve in 10.0 mL of *Phosphate buffer*, and mix. [NOTE— This solution is stable for 4 weeks at 4° .]

Standard preparation— Add about 2 mL of water to a glass weighing bottle, and weigh accurately. Add about 100 mg (about 0.13 mL) of freshly distilled acetaldehyde, and weigh accurately. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water, transferring each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water to volume, and mix. Store at 4° for about 20 hours. Pipet 1 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Test preparation— Transfer about 2 g of Povidone , accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Phosphate buffer*, dilute with *Phosphate buffer* to volume, and mix. Insert a stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Procedure— Pipet 0.5 mL each of the *Standard preparation*, the *Test preparation*, and water to provide the reagent blank into separate 1-cm cells. Add 2.5 mL of *Phosphate buffer* and 0.2 mL of *NAD solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2 to 3 minutes at 22 ± 2° . Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Add 0.05 mL of *Aldehyde dehydrogenase solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 minutes at 22 ± 2° . Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Calculate the percentage of aldehydes, expressed as acetaldehyde, in the Povidone taken by the formula:

$$10(C/W) \left[\frac{(A_{U2} - A_{U1}) - (A_{S2} - A_{S1})}{(A_{S2} - A_{S1}) - (A_{B2} - A_{B1})} \right],$$

in which C is the concentration, in mg per mL, of acetaldehyde in the *Standard preparation*; W is the weight, in g, of Povidone taken; A_{U1} , A_{S1} , and A_{B1} are the absorbances of the solutions obtained from the *Test preparation*, *Standard preparation*, and water reagent blank, respectively, before addition of the *Aldehyde dehydrogenase solution*; and A_{U2} , A_{S2} , and A_{B2} are the absorbances of the solutions obtained from the *Test preparation*, *Standard preparation*, and water reagent blank, respectively, after addition of the *Aldehyde dehydrogenase solution*: not more than 0.05% is found.

Vinylpyrrolidinone—

Resolution solution— Transfer 10 mg of vinylpyrrolidinone and 500 mg of vinyl acetate, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with methanol to volume. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer an accurately weighed quantity of about 250 mg of Povidone to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Procedure— Separately inject equal volumes (about 50 µL) each of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the vinylpyrrolidinone peak. [NOTE— If necessary, after each injection of the *Test solution*, wash the polymeric

